

## AMENDED SPECIFICATION

Reprinted as amended in accordance with the Decision of the Superintending Examiner acting for the Comptroller-General dated the first day of June 1962, under Section 14, of the Patents Act, 1949.

## PATENT SPECIFICATION

NO DRAWINGS

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862,242

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International Classification:—A61k.

### COMPLETE SPECIFICATION

#### Resin-Drug Salts

5 We, CHEMICAL PRODUCTS LIMITED, a British Company, formerly of 2, The Green, Richmond, Surrey, now of 225, Bath Road, Slough, Buckinghamshire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

10 This invention relates to the preparation of salts capable of giving a continuous and substantially uniform release of a drug, over a relatively long period of time, as a result of action on the salt of the normal contents of the gastro-intestinal tract.

15 Some drugs are capable of acting as a base and of forming, with an appropriate acidic cation exchange resin, a salt which can conveniently be termed a "resinate" of the drug, and it is the object of the present invention to provide a number of such salts.

20 According to the present invention, in a method of producing a drug-resin complex giving slow and even release of the drug when acted upon by the normal contents of the gastro-intestinal tract, an acidic cation exchange resin, in the form of a polystyrene poly-

mer cross linked with divinyl benzene and containing sulphonic acid groups, or a polymerised methacrylic acid cross-linked with divinyl benzene, is reacted with methadone or pethidine or a derivative thereof, acting as a base to form a salt of the drug.

30 Methadone and pethidine are synthetically prepared organic compounds which exhibit a morphine-like activity:

methadone is 6 dimethylamino - 4:4 diphenylheptan-3 one;

40 pethidine is ethyl 1-methyl-4-phenyl piperidine - 4 - carboxylate.

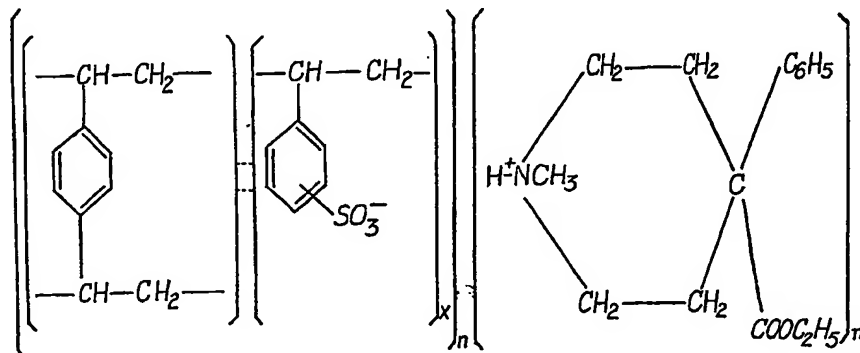
Suitable resins are commercially available, e.g. "Zeokarb 225H" which is the hydrogen form of a polystyrene resin cross-linked with divinyl benzene and containing sulphonic acid groups, and "Zeokarb 226H" which is the hydrogen form of a polymerised methacrylic acid resin, cross-linked with divinyl benzene and containing carboxylic groups.

45 "Zeokarb" is a Registered Trade Mark of The Permutit Company Limited.

50 The salt formed with the sulphonic acid resin and Pethidine may be represented by the following general formula:

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Pethidine resinate



The value  $m/n$  represents the degree of saturation of the resin with the drug, and can be varied. Greater concentration of the drug on the resin may be obtained, for instance, by successive reactions of the resinate salt with further quantities of the drug.

The resins formed are completely insoluble in solvents and are also without odour, but they react with hydrogen chloride (e.g. in the stomach) or sodium chloride (e.g. in the gut) to form the free resin in the hydrogen or sodium form, as the case may be, together with the drug in the hydrochloride form. This reaction is slow when in contact with the concentration of ions in the gastro-intestinal tract of man and thus the salt may be used to produce an evenly sustained therapeutic effect over a relatively extended period of time.

Methadone and pethidine resins are prepared as follows:—

A 5% w/v aqueous solution of the hydrochloride of the drug is prepared accurately and its pH value determined. 100 mls of this solution are reacted with an appropriate quantity of the resin. When the resultant pH value of the solution becomes constant, the insoluble resinate is removed, washed with water until free from chloride ion, washed with acetone, and finally dried at a temperature preferably not exceeding 80° F. until the moisture content does not exceed 2%.

Modifications in the above process may be made as follows:—

- (a) more drug hydrochloride solution may be added to obtain a stronger resinate, i.e. a resinate in which the resin is more nearly saturated with the drug.
- (b) the solution of drug hydrochloride may be prepared in acetone or alcohol.

(c) the drug may be bonded by reaction with the resin in the Na or H form.

Resinate salts produced in this manner are preferably stored in containers which will exclude atmospheric moisture.

#### WHAT WE CLAIM IS:—

1. The method of producing a drug-resin complex giving slow and even release of the drug when acted upon by the normal contents of the gastro-intestinal tract, wherein an acidic cation exchange resin, in the form of a polystyrene polymer cross linked with divinyl benzene and containing sulphonic acid groups, or a polymerised methacrylic acid cross-linked with divinylbenzene, is reacted with methadone or pethidine or a derivative thereof, acting as a base, to form a resinate salt of the drug.

2. The method claimed in claim 1 wherein the drug is used in the form of its hydrochloride in aqueous solution.

3. The method claimed in claim 1 wherein the drug is prepared in solution in acetone or alcohol.

4. The method claimed in any one of the preceding claims, wherein the resinate salt produced is reacted with further quantities of the drug to obtain greater concentration of the drug on the resin.

5. The method of producing methadone resinate, according to claim 1 and as particularly described herein.

6. The method of producing pethidine resinate, according to claim 1 and as particularly described herein.

7. Resinate salts made by the combination of an acidic cation exchange resin in the form of a polystyrene polymer cross linked with divinyl benzene and containing sulphonic acid

groups, or a polymerised methacrylic acid cross-linked with divinylbenzene, with methadone or pethidine or a derivative thereof.

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